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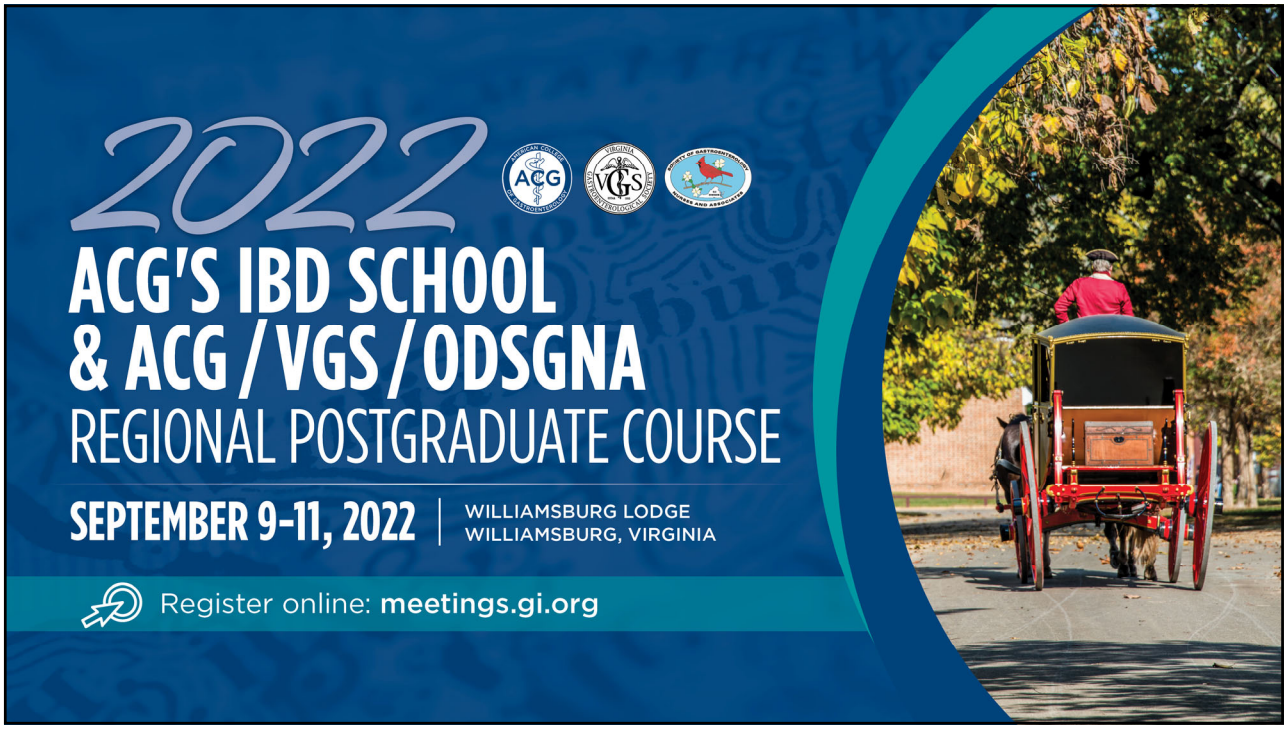
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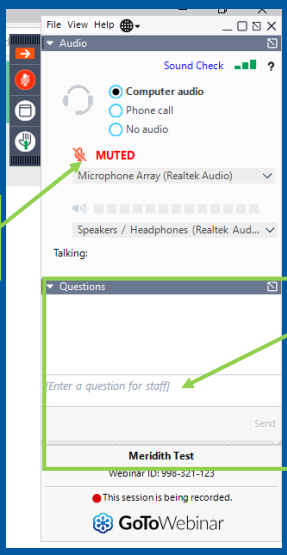
## Participating in the Webinar

All attendees will be muted and will remain in Listen Only Mode.




Type your questions here so that the moderator can see them. Not all questions will be answered but we will get to as many as possible.

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## How to Receive CME and MOC Points

**LIVE VIRTUAL GRAND ROUNDS WEBINAR**

ACG will send a link to a CME & MOC evaluation to all attendees on the live webinar.

**ABIM Board Certified physicians need to complete their MOC activities by December 31, 2022 in order for the MOC points to count toward any MOC requirements that are due by the end of the year. No MOC credit may be awarded after March 1, 2023 for this activity.**

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## MOC QUESTION

If you plan to claim MOC Points for this activity, you will be asked to: Please list specific changes you will make in your practice as a result of the information you received from this activity.

Include specific strategies or changes that you plan to implement.
THESE ANSWERS WILL BE REVIEWED.

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## ACG Virtual Grand Rounds

**Join us for upcoming Virtual Grand Rounds!**

**Week 34 – Thursday, August 25, 2022**
**Update on the Management of Anticoagulants and Antiplatelet Guidelines**
Faculty: Neena S. Abraham, MD, MSc (Epid), FACG
Moderator: Bryan G. Sauer, MD, MSc (Clin Res), FACG
Thursday, August 25th at Noon Eastern and **NEW! 8pm Eastern!**

**Week 35 – Thursday, September 1, 2022**
**ID for the GI – GI Presentations of Unusual Infections**
Faculty: Mark S. Riddle, MD, DrPH
Moderator: Freddy Caldera, DO, MS, FACG
Thursday, September 1st at Noon Eastern and **NEW! 8pm Eastern!**

Visit **gi.org/ACGVGR** to Register

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# Disclosures

**Jasmohan S. Bajaj, MD, MS, FACG**
Bausch: Grant/Research Support
Biovie: Grant/Research Support
Cosmo Pharmaceuticals: Grant/Research Support
Grifols: Grant/Research Support
Mallinckrodt Pharmaceuticals: Grant/Research Support
Norgine: Advisory Committee/Board Member (Ended October 1, 2021)
Sequana: Grant/Research Support

**David E. Bernstein, MD, MACG**
AbbVie: Consultant, Grant/Research Support
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**All of the relevant financial relationships listed for these individuals have been mitigated*

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# Acute-on-Chronic Liver Disease

Jasmohan S. Bajaj, MD, MS, FACG
Professor of Medicine,
Division of Gastroenterology, Hepatology and Nutrition
Virginia Commonwealth University and
Central Virginia Veterans Healthcare System
Richmond, Virginia

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## Acute-on-Chronic Liver Failure Clinical Guidelines

Jasmohan S. Bajaj, MD, MS[1], Jacqueline G. O'Leary, MD, MPH[2], Jennifer C. Lai, MD, MBA[3], Florence Wong, MD[4], Millie D. Long, MD, MPH (Methodologist)[5], Robert J. Wong, MD (Methodologist)[6] and Patrick S. Kamath, MD[7]

**In patients with cirrhosis and chronic liver disease, acute-on-chronic liver failure is emerging as a major cause of mortality. These guidelines indicate the preferred approach to the management of patients with acute-on-chronic liver failure and represent the official practice recommendations of the American College of Gastroenterology. The scientific evidence for these guidelines was evaluated using the Grading of Recommendations, Assessment, Development, and Evaluation process. In instances where the evidence was not appropriate for Grading of Recommendations, Assessment, Development, and Evaluation, but there was consensus of significant clinical merit, "key concept" statements were developed using expert consensus. These guidelines are meant to be broadly applicable and should be viewed as the preferred, but not only, approach to clinical scenarios.**

*Am J Gastroenterol 2021;00:1–27. https://doi.org/10.14309/ajg.0000000000001595; published online XXX*

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## Important questions

- What is acute on chronic liver disease or failure and how is it it different from decompensated cirrhosis and from acute liver failure?
- How do we define and prognosticate patients with ACLF?
- What are the precipitants and potential prevention strategies?
- What are the individual organ failures that we need to focus on?
- Should ACLF patients be given priority for liver transplant?
- What are the future directions?

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## Case- ER presentation

- A 59-year-old man is brought to the emergency room (ER) by his wife for new onset confusion and increased abdominal girth. Past medical history is notable for uncontrolled diabetes, obesity, and social alcohol use.
- On examination he is afebrile, alert, and oriented only to place. Abdominal examination revealed a fluid wave.
- He has not sought outpatient care for 3 years, although he underwent emergency surgery for a strangulated inguinal hernia 6 weeks ago.
- At hospital discharge, a PPI was initiated for “prophylaxis”.
- Notable admission labs include a serum creatinine 1.3 mg/dL, bilirubin 2 mg/dL, albumin 3.1g/dL, INR 1.4, WBC count 7000/mL, and platelet count $105x10^9$/L.

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## Case- Initial Work-up

- The patient has been in the ER for 8 hours and is finally admitted with diagnoses of cirrhosis, ascites, and HE. He is started on lactulose with some improvement in mental status but still has asterixis the next morning.
- Fourteen hours after initial presentation, a diagnostic paracentesis shows spontaneous bacterial peritonitis (SBP).
- His serum creatinine and WBC count have increased to 1.8 mg/dL and 8600/mL respectively.
- The urinalysis is bland, and renal sonogram is normal. He is started on IV ceftriaxone 2gm daily and IV 25% salt-poor albumin.

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## Case- 48 hours later

- Still disoriented despite ceftriaxone for 48 hours, with new onset-shortness of breath.
- Creatinine is now 3.0mg/dL, sodium 130 mEq/L, bilirubin 3.5 mg/dL and INR 1.8.
- A repeat tap shows a <25% reduction in PMNs. Blood and ascitic fluid cultures from the ER are negative.
- IV norepinephrine is initiated (since terlipressin is not currently available in the US). Antibiotics are escalated to meropenem and vancomycin since the ascites PMNs have not decreased by ≥ 25%.

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# Case- Next Morning

- Tachypneic and hypoxic (SpO2: 91%) with a new RLL infiltrate
- Obtunded, anuric with a MAP of 45mmHg. He is transferred to the ICU with a serum creatinine of 4.8 mg/dL and WBC count of 15000/mL.
- Discussions regarding intubation, renal replacement therapy (RRT), and pressor support are undertaken with his wife. Since he now requires organ support to maintain perfusion, oxygenation, and is obtunded, he is a suboptimal candidate for liver transplantation
- Ultimately the patient passes away without liver transplant.

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Dominoes fall rapidly if precipitants for ACLF are not recognized early

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# Pathogenesis and Definitions

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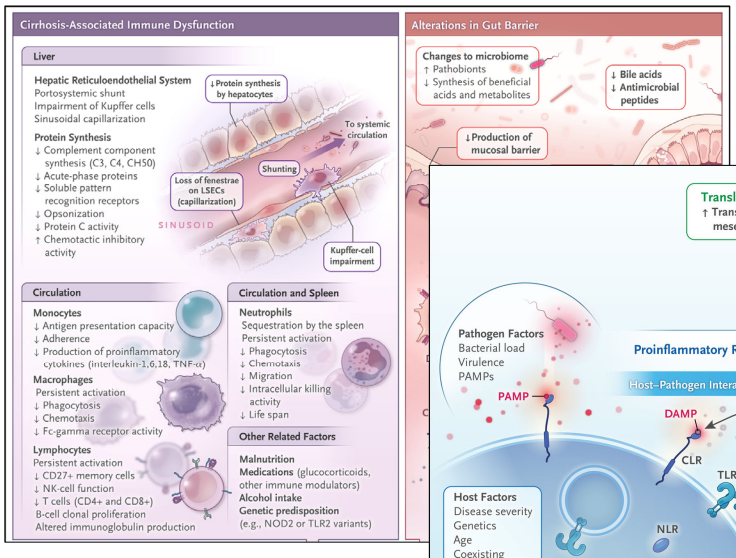
## Gut-liver changes and immune dysfunction




Albillos et al J Hep 2020, Bajaj et al NEJM 2021

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## Acute liver failure vs ACLF

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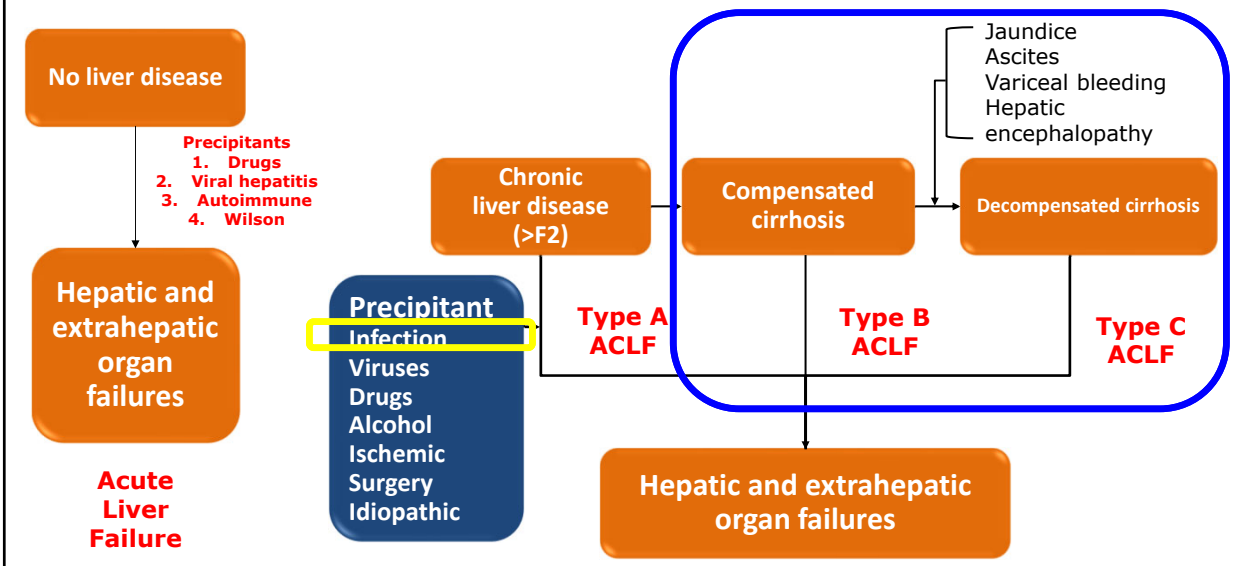


Jalan R et al ACLF WGO Consensus Gastroenterology 2014

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| Organ | APASL ACLF Research Consortium | EASL CLIF-C ACLF | NACSELD |
|---|---|---|---|
| Liver | Total Bilirubin PT/INR | Total bilirubin PT/INR | -- |
| Kidney | Creatinine | Creatinine/Dialysis | Dialysis |
| Brain | HE grade | HE grade | HE grade III/IV |
| Circulatory | Lactate | MAP, vasopressors | MAP, vasopressors |
| Respiratory | -- | $PaO_2$ or $SpO_2$ / $FiO_2$ | Mechanical ventilation |
| Major Organ failure Category | Predominantly Hepatic failure variables | Combination of hepatic and extrahepatic organ failure variables | Predominantly extra-hepatic organ failure variables |
| Issues | Diagnosis can be made early enough for intervention to alter disease course. Sensitive but not specific for early mortality | Diagnosis of ACLF may be made too late to impact disease outcome. | Diagnosis of ACLF may be made too late to impact disease outcome. |

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# ACG ACLF definition

ACLF is a potentially reversible condition in patients with chronic liver disease with or without cirrhosis that is associated with the potential for multiple organ failure and mortality within 3 months in the absence of treatment of the underlying liver disease, liver support, or liver transplantation

Bajaj JS et al ACG ACLF Guidelines 2021

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# ACG Guideline Concept Statements

1. In patients with cirrhosis who are hospitalized, the NACSELD score is likely associated with futility while the EASL-CLIF SOFA score is associated with 28-day prognostication.
2. None of the three society definitions is optimal for informing management change.
3. Prognostic markers that predict ACLF outcome should be separate from diagnostic markers that confirm the presence of ACLF.
4. Microbial composition and microbial-origin metabolites can be used as biomarkers for ACLF development and prognosis with further validation.

Bajaj JS et al ACG ACLF Guidelines 2021

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# Individual Organ Failures

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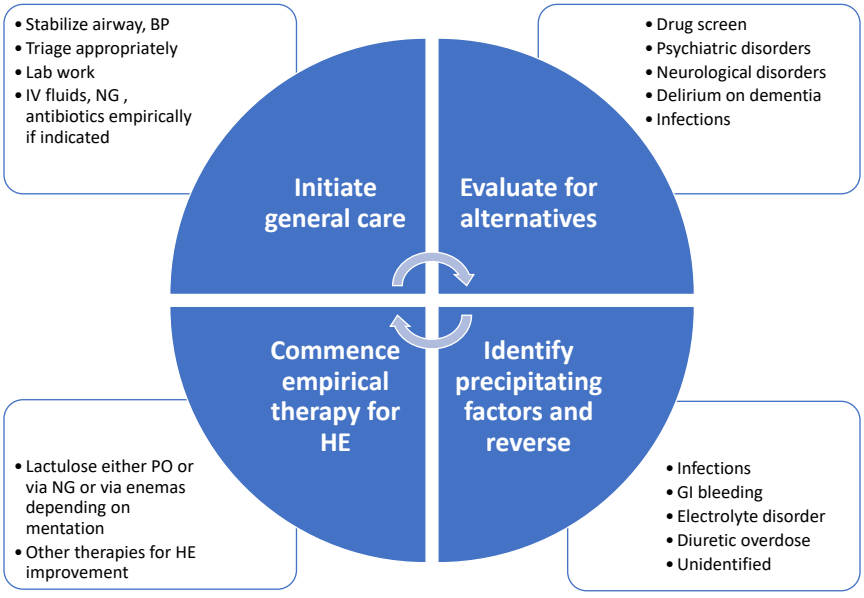
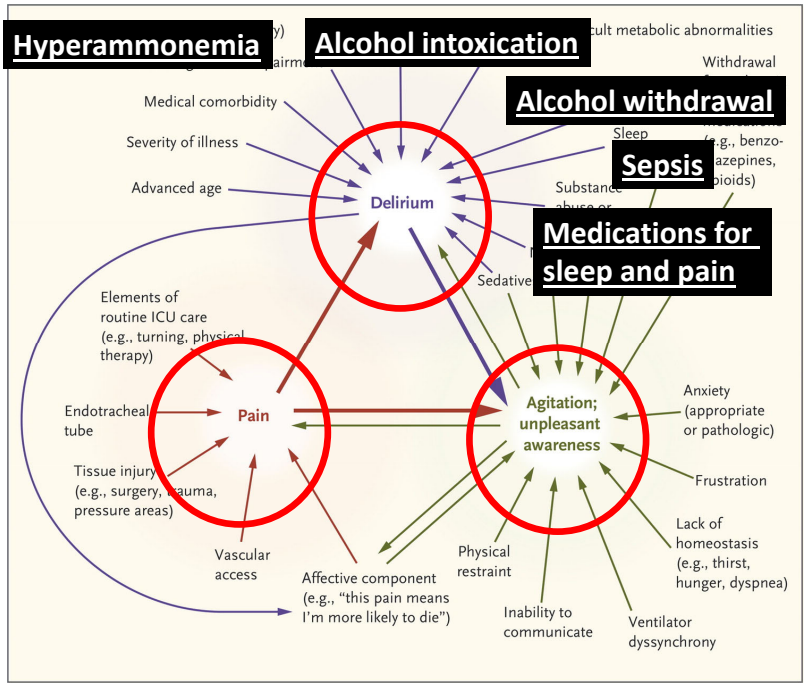
## Brain Failure or Acute Encephalopathy: Mostly HE




Acharya et al Am J Gastro 2018

26




- In ACLF, use of short-acting dexmedetomidine for sedation vs other agents to shorten time to extubation.
- In ventilated patients, we suggest against prophylactic antibiotics to reduce mortality or duration of mechanical ventilation

**Reade et al NEJM 2015**
**ACG ACLF Guidelines 2021**

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| | |
|---|---|
| **AKI Definition** | Increase in sCr 0.3 mg/dl ≤48 hours or 50% increase from baseline |
| **AKI Staging** | **Stage 1**: Increase in sCr 0.3 mg/dl in ≤48 hours<br>OR Increase in sCr ≥1.5-2.0 times from baseline<br>**Stage 2**: Increase in sCr ≥2.0-3.0 times from baseline<br>**Stage 3**: Increase in sCr ≥3.0 times from baseline OR<br>Serum creatinine 4.0mg/dl with an acute increase of 0.3 mg/dl<br>OR<br>Initiation of renal replacement therapy |
| **HRS-AKI** | |
| **Diagnostic Criteria** | -Cirrhosis and ascites;<br>-Stage 2 or 3 AKI;<br>-No improvement of serum creatinine (decrease of creatinine ≤ 0.3mg/dl of baseline) after at least 48 hours of diuretic withdrawal and volume expansion with albumin (1 g/kg body weight/day for 2 days);<br>-Absence of hypovolemic shock or severe infection requiring vasoactive drugs to maintain arterial pressure;<br>-No current or recent treatment with nephrotoxic drugs;<br>-Proteinuria <500 mg/day and no microhematuria (<50 RBCs/ml). |

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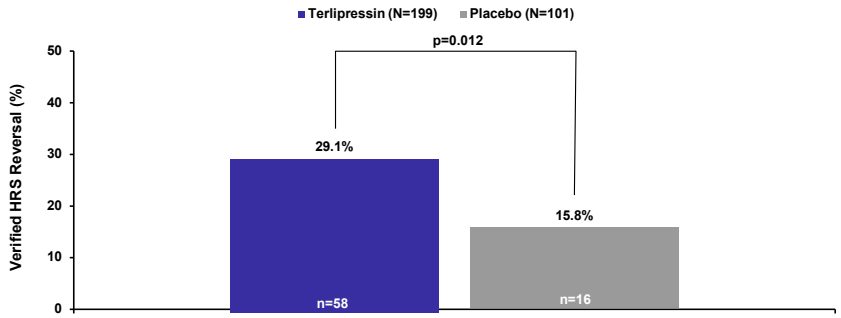
## Terlipressin increases HRS reversal




- No overall survival benefit but trend for improved RRT-free survival and significant improvement in post-OLT survival
- Serum creatinine > 5 mg/dl associated with low response and increased deaths (70 vs 47%) with terlipressin
- Reduced need for RRT with terlipressin

Wong et al, NEJM 2021

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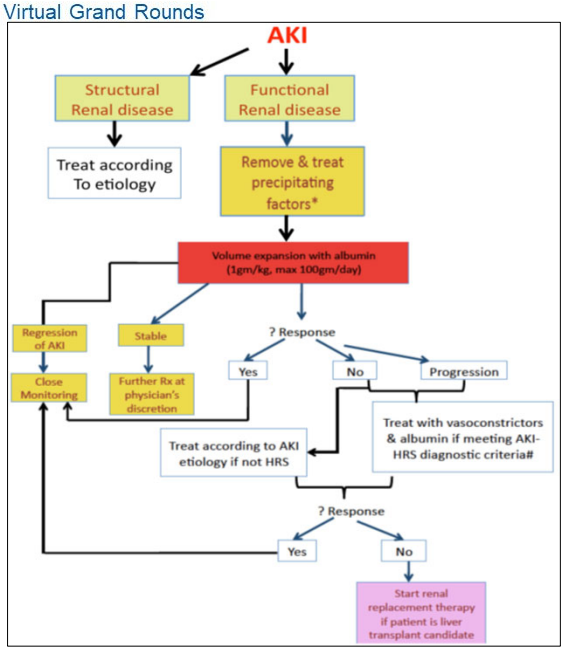


1. In AKI stage 2 & 3 acute kidney injury (AKI), we suggest IV albumin and vasoconstrictors vs albumin alone
2. In hospitalized patients HRS-AKI without high grade of ACLF or major cardiopulmonary or vascular disease, we suggest terlipressin or norepinephrine to improve renal function.

Wong et al 2016, Wong et al NEJM 2021

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## Coagulation Failure: INR is not the be-all and end-all

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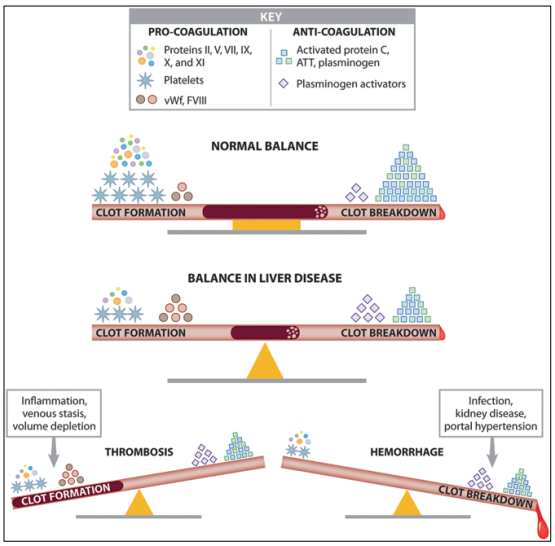


1. In ACLF, we suggest against INR to measure coagulation risk
2. In patients with ACLF and altered coagulation parameters, we suggest against transfusion in the absence of bleeding or a planned procedure.
3. In patients who require invasive procedures, we recommend the use of Thrombo-elastography (TEG) or rotational TEG (ROTEM), vs INR, to accurately assess transfusion needs.

Northup et al 2015, O'Leary et al 2019

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## Precipitating Factors

- Infections
- Alcohol-related
- Surgery (Mayo Clinic and Vocal Penn Score)
- Drug-induced liver injury
- Viral hepatitis, including reactivation and flare

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## Infections lead to high mortality in cirrhosis

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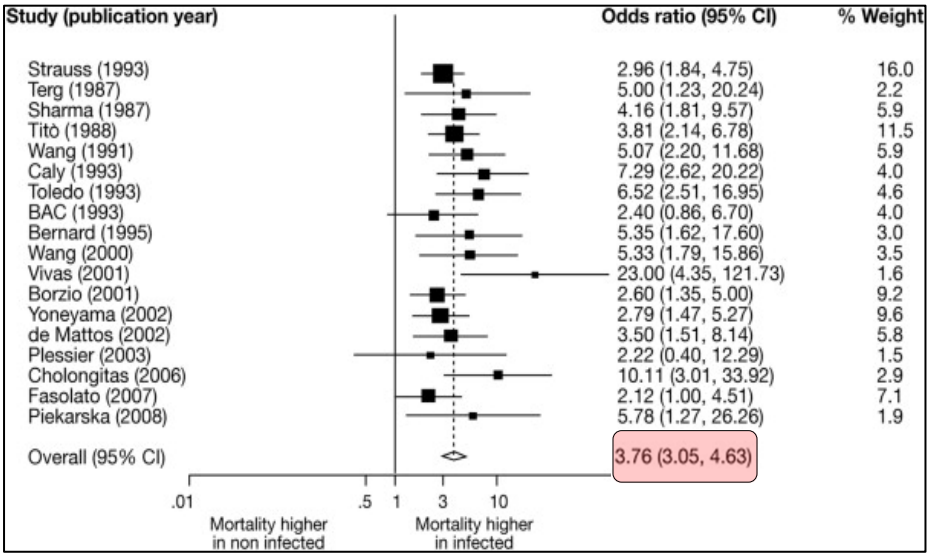


30% die within 1 month

Additional 30% die by 1 year

Arvaniti V et al. Gastroenterology 2010; 139: 1246-1256

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## Clues that can indicate infections in cirrhosis

- Usual signs of infection may be absent due to impaired immune response
- Other signs and symptoms could be relevant
  - Altered mental status or hepatic encephalopathy
  - Acute kidney injury
  - Asymptomatic patients with ascites can have “silent” SBP
  - Increase in WBC count may not be dramatic since cirrhotic patients have a lower baseline

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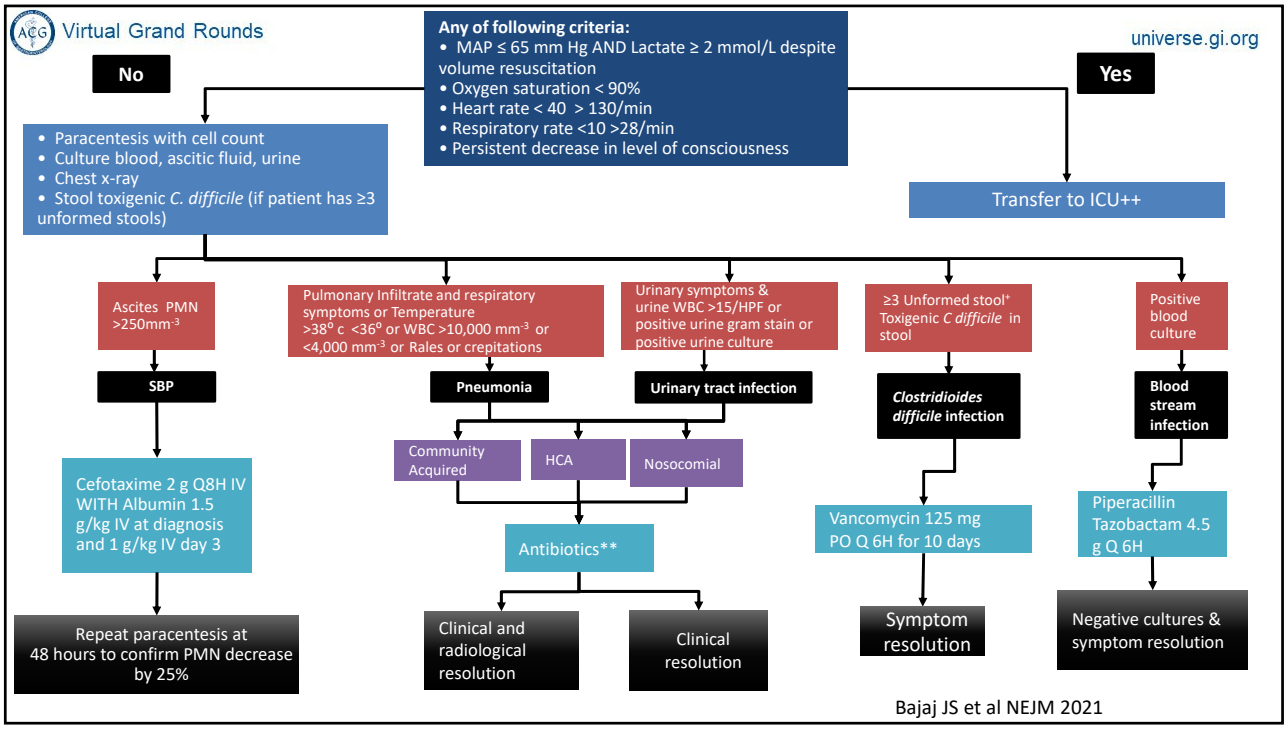
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Any of following criteria:
• MAP ≤ 65 mm Hg AND Lactate ≥ 2 mmol/L despite volume resuscitation
• Oxygen saturation < 90%
• Heart rate < 40 > 130/min
• Respiratory rate <10 >28/min
• Persistent decrease in level of consciousness
No
Yes
• Paracentesis with cell count
• Culture blood, ascitic fluid, urine
• Chest x-ray
• Stool toxigenic C. difficile (if patient has ≥3 unformed stools)
Transfer to ICU++
Ascites PMN >250mm-3
Pulmonary Infiltrate and respiratory symptoms or Temperature >38° c <36° or WBC >10,000 mm-3 or <4,000 mm-3 or Rales or crepitations
Urinary symptoms & urine WBC >15/HPF or positive urine gram stain or positive urine culture
≥3 Unformed stool+ Toxigenic C difficile in stool
Positive blood culture
SBP
Pneumonia
Urinary tract infection
Clostridioides difficile infection
Blood stream infection
Community Acquired
HCA
Nosocomial
Cefotaxime 2 g Q8H IV WITH Albumin 1.5 g/kg IV at diagnosis and 1 g/kg IV day 3
Antibiotics**
Vancomycin 125 mg PO Q 6H for 10 days
Piperacillin Tazobactam 4.5 g Q 6H
Repeat paracentesis at 48 hours to confirm PMN decrease by 25%
Clinical and radiological resolution
Clinical resolution
Symptom resolution
Negative cultures & symptom resolution
Bajaj JS et al NEJM 2021

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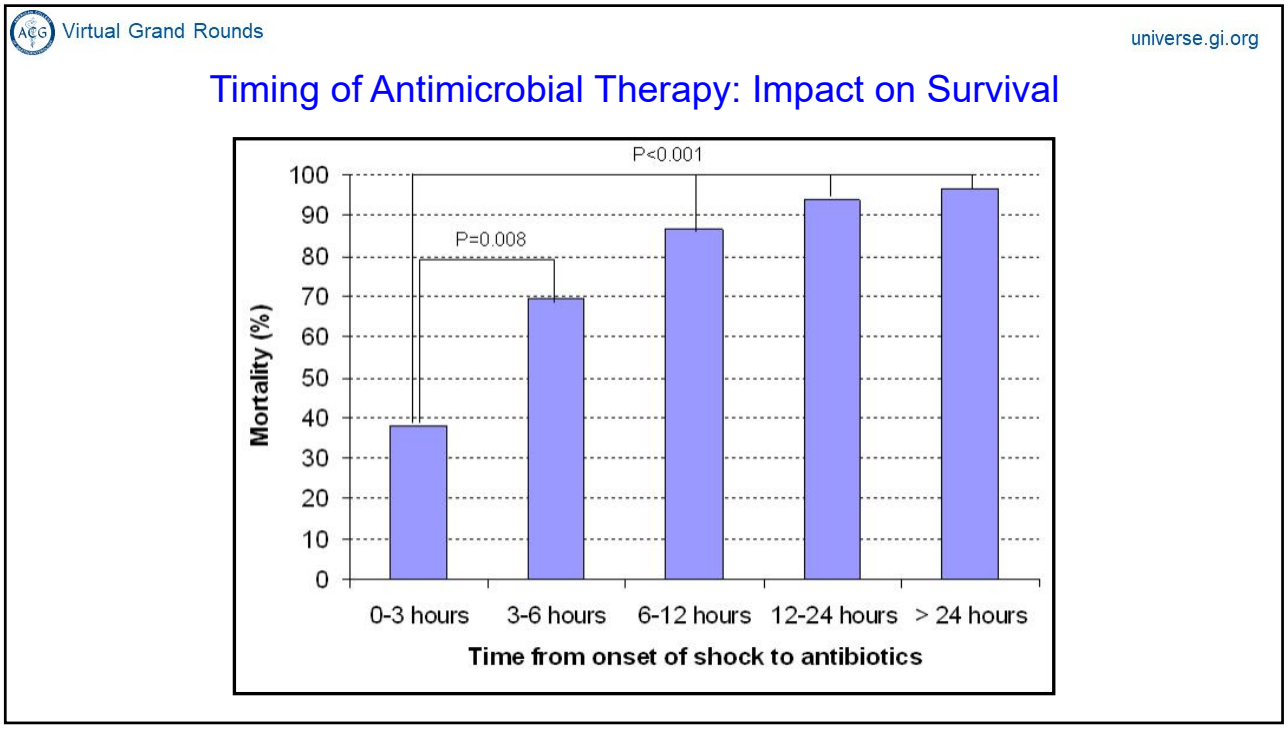
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Timing of Antimicrobial Therapy: Impact on Survival
P<0.001
P=0.008
Mortality (%)
100
90
80
70
60
50
40
30
20
10
0
0-3 hours
3-6 hours
6-12 hours
12-24 hours
> 24 hours
Time from onset of shock to antibiotics

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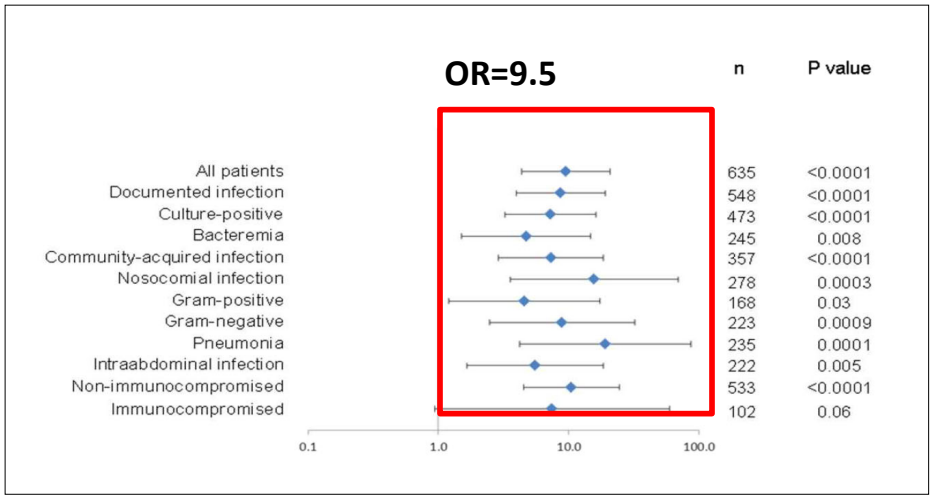
## Inappropriate antibiotics increase mortality




- **Risk factor: Multidrug resistance organism**

Arabi YM et al. Hepatology, Accepted 2012

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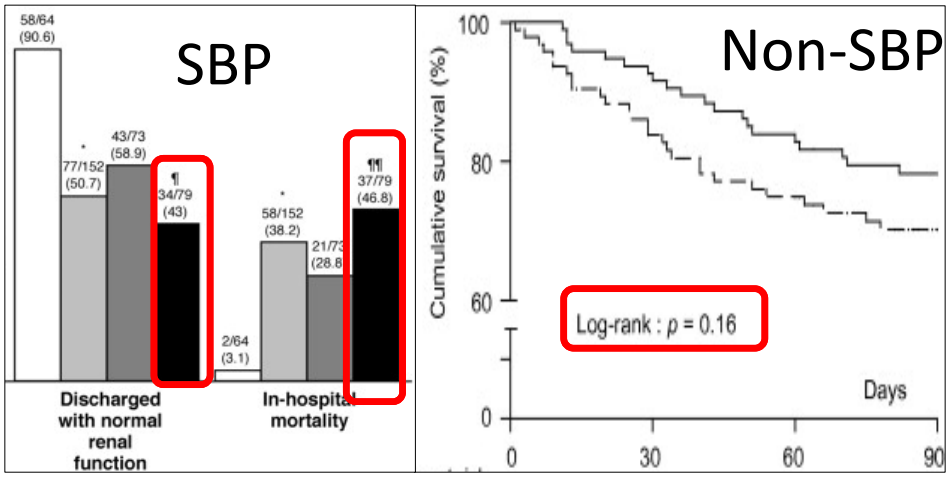
## Judicious use of albumin prevents mortality and AKI in SBP but not in other infections and not for all inpatients




Poca et al J Hepatol 2012, Sort et al N Engl J Med 1999, Thevenot et al J Hepatol 2014, China L et al NEJM 2021

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## ACG ACLF Guideline Recommendations: Infections

- Check for infection in hospitalized patients.
- In suspected infection, we suggest early antibiotics
- In patients not responding to antibiotic therapy, we recommend suspicion of a resistant organism or fungal infection
- In SBP albumin with antibiotics to prevent AKI and subsequent organ failures but not in other infections.
- In with prior SBP, we suggest use of antibiotics for secondary SBP prophylaxis to prevent recurrent SBP.
- In those needing primary SBP prophylaxis, we suggest daily prophylactic antibiotics, although no one specific regimen is superior to another, to prevent SBP
- We suggest avoiding PPI unless there is a clear indication

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## Therapeutic strategies

- General (airway, multi-disciplinary team, nutrition, treating precipitating factors)
- Specific treatments (albumin, G-CSF, Stem cell therapy)
- Liver-assist devices (MARS, ELAD)
- Liver transplant (deceased or living donor)

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If no resolution or condition worsens after initial Rx

Family Meeting/Decision

End of life care

Transfer to ICU++

Investigations → Paracentesis, Culture blood, ascitic fluid, urine, Chest x-ray

Treat infection → Vancomycin 15 mg/kg Q 6 H; Meropenem 1 gram Q 8 H

General measures → Enteral nutrition is preferred; Fluid resuscitation within 3 hours; Therapeutic paracentesis; Aspiration precautions; DVT prophylaxis; Stress ulcer prophylaxis

MAP <60 mg Hg → Norepinephrine Range: 0.125 to 0.2 mcg/kg/minute

MAP <60 Hg Persistent shock → Hydrocortisone 50 mg Q 6 h

Bajaj JS et al NEJM 2021

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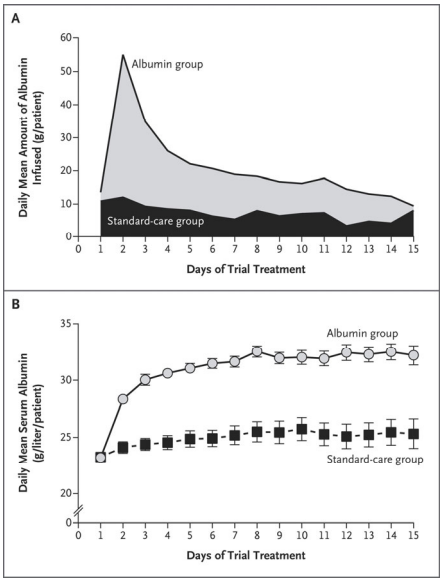
## Albumin in Inpatients with Cirrhosis: Not Helpful




- 777 inpatients across multiple UK Centers
- Open-label randomized trial
- Albumin targeted to 3g/dl or standard of care for 14 days

**Primary Endpoint: new infection, kidney dysfunction, or death between days 3 and 15 after the initiation of treatment.**

**Results: No significant change but higher respiratory failure in albumin arm**

ACG Recommendations: We recommend against daily infusion of albumin to maintain albumin >3 gm/dl to improve mortality, prevention of renal dysfunction or infection

China et al NEJM 2021

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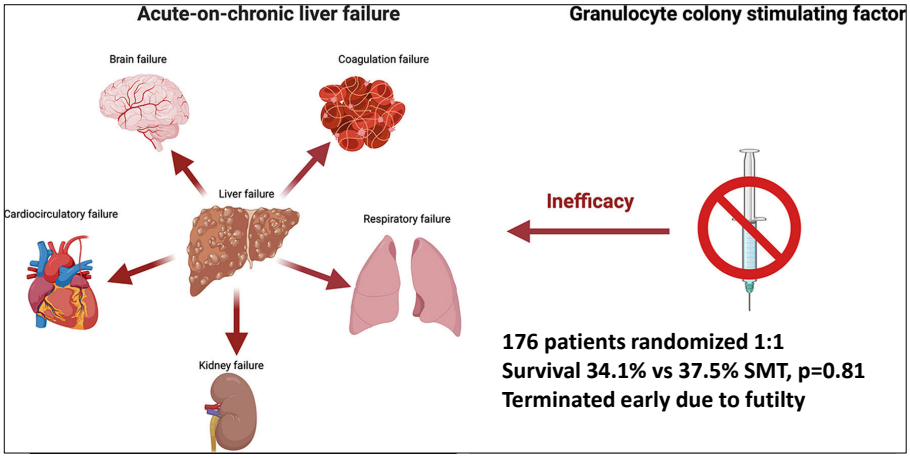
# G-CSF and effect on liver disease severity




ACG Recommendations: In ACLF, we suggest against the use of G-CSF to improve mortality

Kedarisetty CK et al Gastro 2015, Engelmann et al J Hepatol 2021

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# Should ACLF patients get extra listing priority for liver transplant?

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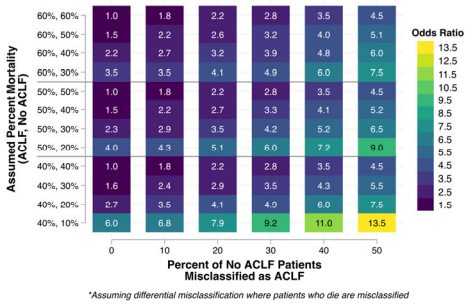
## Arguments against prioritizing




| Organ failure | EASL-CLIF | NACSELD | Data in UNOS registry* |
|---|---|---|---|
| Liver | Bilirubin ≥12mg/dL | N/A | Serum bilirubin |
| Kidney | Creatinine ≥1.5 md/dL (or >2mg/dL)† | Renal replacement therapy | Serum creatinine and dialysis in last week (yes/no) |
| Brain | HE West Haven grades III/IV | HE West Haven grades III/IV | None, grade 1-2, grade 3-4 |
| Coag | INR ≥2.5 | N/A | Serum INR |
| Respiration | Mechanical ventilation + $PaO_2/FiO_2$≤200 or $SpO_2/FiO_2$≤214 | BiPAP or mechanical ventilation | On ventilator (yes/no) |
| Circulation | Use of vasopressors | Vasopressors + MAP<60mmHg or SBP reduction >40mmHg despite adequate resuscitation | Inotropes (yes/no); life support (yes/no) |

1. Potential for misclassification of UNOS data vs ACLF grade
2. Using retrospective data to make prospective decisions
3. Zero –sum game; non-ACLF pts may be affected
4. Currently there is low support to change listing and priority criteria

Goldberg & Bajaj Liver Transpl 2021, Bajaj & Verna Liver Transpl 2020

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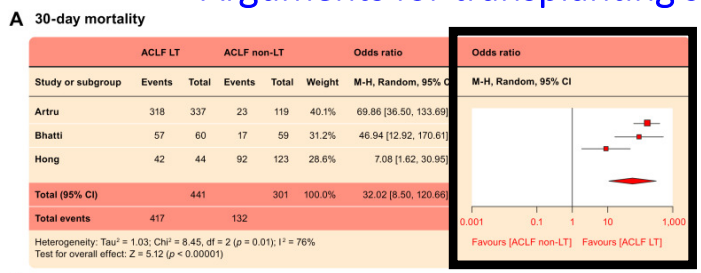
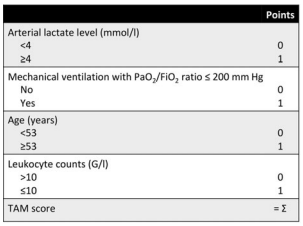
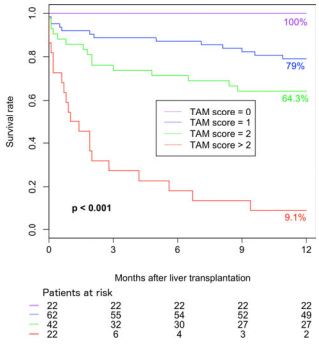
## Arguments for transplanting selected ACLF patients




1. MELD may not capture the disease severity
2. Acceptable survival post-LT for ACLF-2 and 3
3. Futility rules may need to be specified




**TAM score:**
a. Age ≥53 years,
b. arterial lactate ≥4 mmol/L
c. mechanical ventilation with $PaO_2/FiO_2$ ≤ 200 mm Hg,
d. leukocyte count ≤10 G/L

Jalan et al J Hepatol 2021, Artzner et al AJT 2020

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## Transplant versus Futility for ACLF: ACG Guideline recommendations

- ACLF patients who continue to require mechanical ventilation due to ARDS or brain-related conditions despite optimal therapy, we suggest against LT listing
- In patients with end-stage liver disease admitted to the hospital, we suggest early goals of care discussion and if appropriate, referral to palliative care to improve resource utilization

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## Future Directions

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## What is needed in a biomarker for ACLF?

**(a) objective,**
**(b) reliable,**
**(c) specific to ACLF and distinct from AD and from other patients without cirrhosis requiring critical care,**
**(d) easily translatable into clinical practice,**
**(e) determine who is a good candidate for liver transplantation.**

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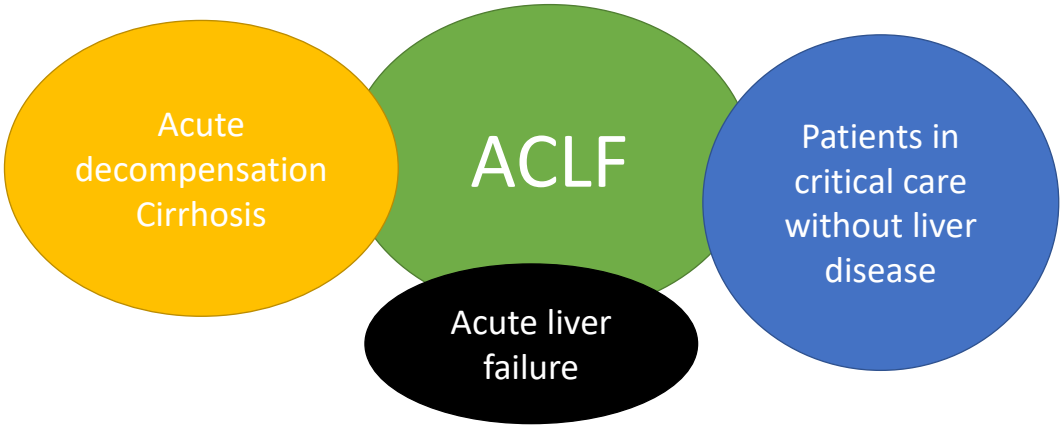
## Issues with current ACLF definitions & biomarkers

- Discordance as to underlying liver disease severity and precipitating factors
- Not prognostic but diagnostic because end-organ failures are likely related to death
- Need to be more pro-active rather than reactive

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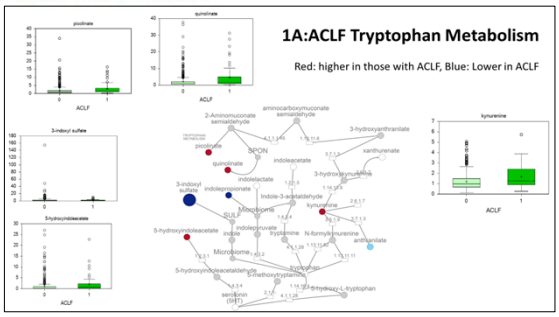
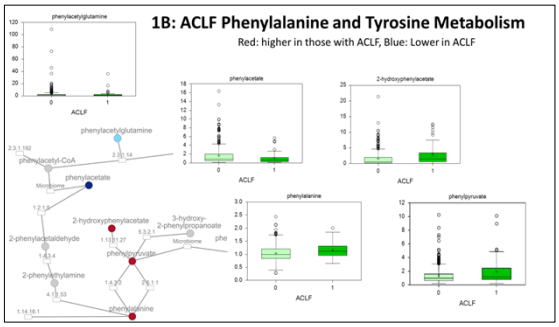
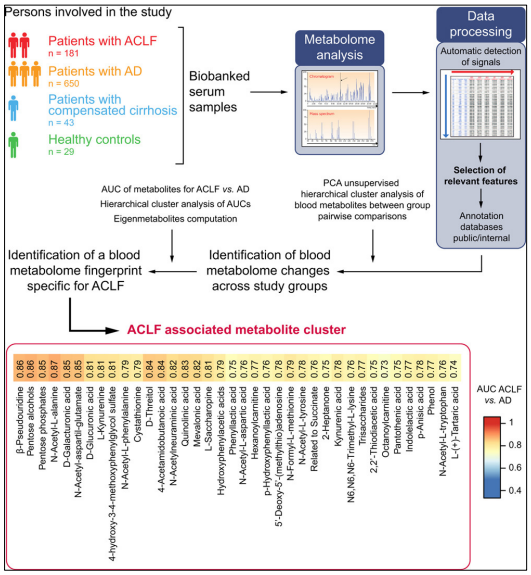



**Microbial-origin Metabolites**

1. **Differentiate between patients with/without ACLF**
2. **Can independently predict who develops ACLF**




Bajaj JS et al Gastroenterology 2020, Moreau et al J Hepatol 2020

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# Back to the case: Opportunities missed that can snowball into ACLF

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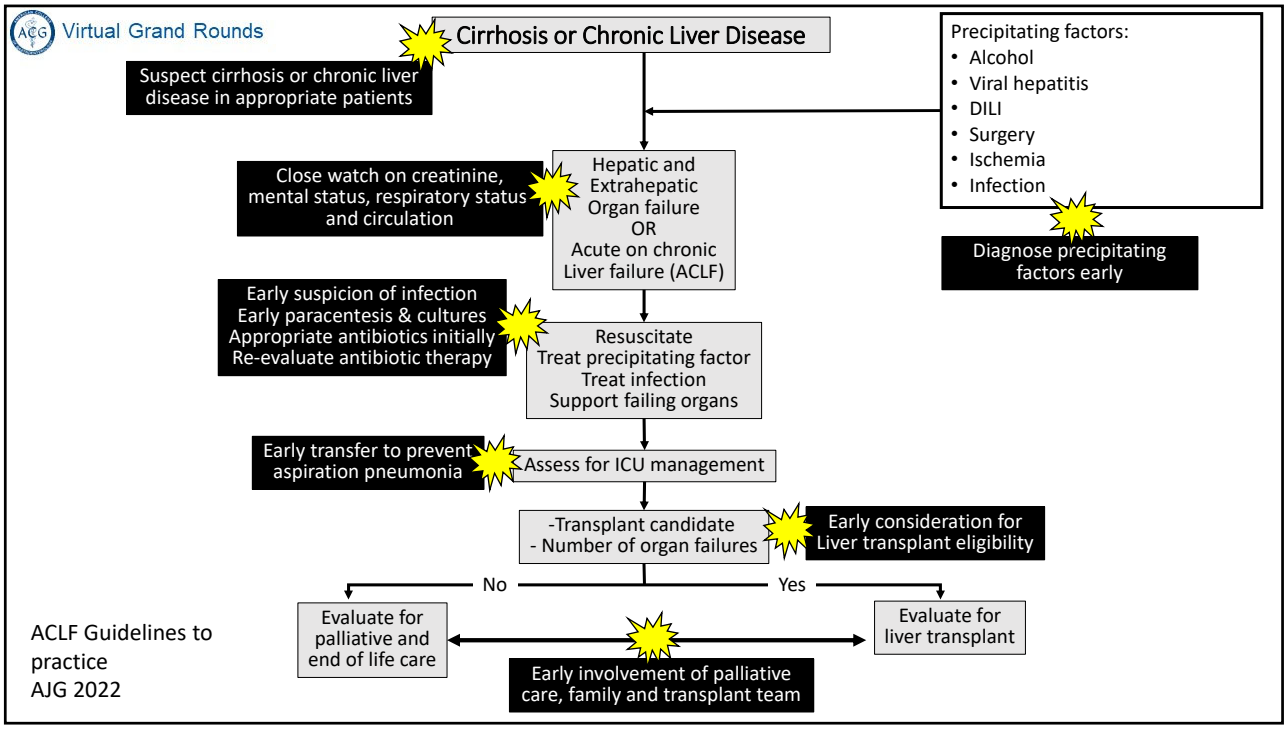


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# Summary and Take-Home Messages

- ACLF represents an increasingly large healthcare and economic burden in the US with a high mortality
- Infections are one of the major reasons for ACLF, and their bacteriology of infections is changing radically.
- A high index of suspicion, flexible, rapid and appropriate antibiotics and prevention of acute kidney injury is required to prevent ACLF from infections
- Avoid unnecessary PPIs
- Need for systematic efforts to improve patient outcomes (risk factor modification, early diagnosis, effective treatment)
- Cost-effective strategies towards higher recovery, less mortality are needed, especially in the context of liver transplant

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# Acute-on-Chronic Liver Failure Clinical Guidelines

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**In patients with cirrhosis and chronic liver disease, acute-on-chronic liver failure is emerging as a major cause of mortality. These guidelines indicate the preferred approach to the management of patients with acute-on-chronic liver failure and represent the official practice recommendations of the American College of Gastroenterology. The scientific evidence for these guidelines was evaluated using the Grading of Recommendations, Assessment, Development, and Evaluation process. In instances where the evidence was not appropriate for Grading of Recommendations, Assessment, Development, and Evaluation, but there was consensus of significant clinical merit, "key concept" statements were developed using expert consensus. These guidelines are meant to be broadly applicable and should be viewed as the preferred, but not only, approach to clinical scenarios.**

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# Questions and Answers

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